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Amino- and Hydroxy-Functionalized 11-Azaartemisinins and Their Derivatives

Ajit Shankar Singh,[†] Ved Prakash Verma,[†] Mohammad Hassam,[†] Naikade Niraj Krishna,[†] Sunil K. Puri,[‡] and Chandan Singh*[,†]

Division of Medicinal and Process Chemistry and Division of Parasitology, Central Drug Research Institute, Lucknow-226001, India

chandancdri@yahoo.com

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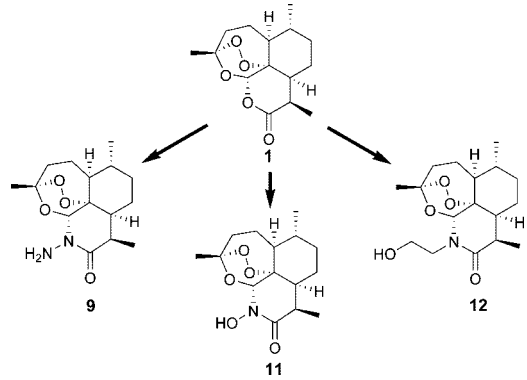
ABSTRACT



An efficient conversion of artemisinin 1 into three new amino- and hydroxy-functionalized 11-aza prototypes 9, 11, and 12 has been achieved on a multigram scale by reaction with hydrazine, hydroxylamine, and 2-amino ethanol, respectively. Of these, 9 has been further diversified into a wide range of derivatives including imines, amines, amides, and linker based dimers. Prototypes 11 and 12 have been converted into the corresponding ethers in high yields. Some of these compounds have shown a high order of activity against multidrug-resistant malaria in mice by oral route.

The discovery of artemisinin **1** as the active principle of the Chinese traditional drug *Artemisia annua* is a major milestone in malaria chemotherapy.[1] Artemisinin and its more potent semisynthetic derivatives, e.g., artemether **2**, arteether **3**, and artesunic acid **4**, are effective against both chloroquine-sensitive and chloroquine-resistant malaria (Figure 1).

These compounds are fast acting and are currently the drugs of choice for the treatment of cerebral/complicated malaria caused by multidrug-resistant *Plasmodium falciparum*.[2] While these drugs show excellent activity by

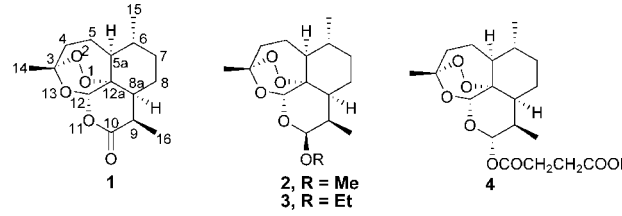


Figure 1. Artemisinin and its derivatives.

[†] Division of Medicinal and Process Chemistry.
[‡] Division of Parasitology.

(1) (a) Klayman, D. L. *Science* **1985**, *228*, 1049–1055. (b) Luo, X. D.; Shen, C. C. *Med. Res. Rev.* **1987**, *7*, 29–52. (c) Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 253–297. (d) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1651–1681. (e) Borstnik, K.; Paik, I.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol* **2002**, *32*, 1661–1667. (f) Ploypradith, P. *Acta Trop.* **2004**, *89*, 329–342. (g) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945–2964. (h) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425–448. (i) Jefford, C. W. *Drug Discovery Today* **2007**, *12*, 487–494.

(2) Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301–315.

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parenteral route, they show poor absorption by oral route. The extra acetal−lactone or acetal−acetal linkages are linked with their poor hydrolytic stability and therefore poor absorption by oral route. Therefore, conversion of artemisinin to its orally active derivatives has been an objective of several recent studies.[3]

Relevant to the present studies is the conversion of artemisinin to its aza derivatives, e.g., **5**−**8** (Figure 2), by Ziffer et al. and Haynes et al.[4−6]

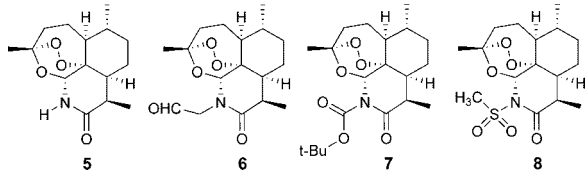
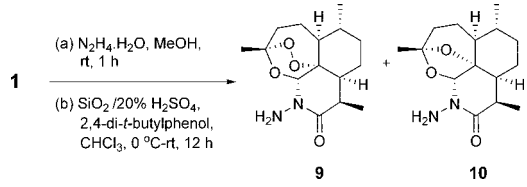


Figure 2. Aza derivatives of artemisinin.

These aza derivatives have shown a better activity profile than that of aretmisinin. In these derivatives, however, nitrogen is in the form of an amide group and only limited number of derivatives can be made. Herein, we report, an efficient two step conversion of artemisinin **1** into three new 11-azaartemisinin prototypes **9**, **11**, and **12** with either a free amino or a free hydroxyl functionality and their subsequent derivatization.

Our strategy to prepare *N*-amino-11-azaartemisinin **9** is shown in Scheme 1. Accordingly, artemisinin **1** was reacted

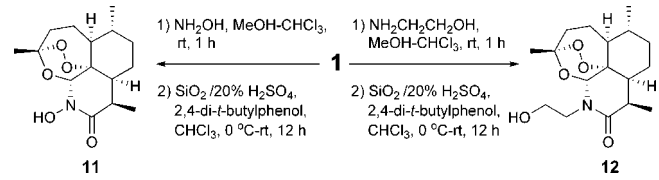
Scheme 1. Synthesis of *N*-Amino-11-azaartemisinin **9**



with hydrazine hydrate in MeOH at rt for 1 h, followed by stirring with silica gel and 20% H_2SO_4 in the presence of 2,4-di-*tert*-butylphenol in $CHCl_3$ to furnish a mixture of *N*-amino-11-azaartemisinin **9** and its deoxy analogue *N*-amino-10-azadeoxyartemisinin **10**, in a combined yield of 59% and in the ratio of 3:7. The yield of *N*-amino-11-azaartemisinin **9** improved to 70% when the first step of the reaction sequence was conducted in MeOH−$CHCl_3$ (7:3) for 1 h at 0 °C; no deoxy analogue was formed under these conditions.

Similarly, the reaction of artemisinin **1** with hydroxylamine and 2-aminoethanol[7] in MeOH−$CHCl_3$ for 1 h at 0 °C followed by treatment with SiO_2/20% H_2SO_4 in the presence of 2,4-di-*tert*-butylphenol in $CHCl_3$ furnished aza derivatives, *N*-hydroxy-11-azaartemisinin **11**, and *N*-ethanol-11-azaartemisinin **12** in 45% and 52% yields, respectively (Scheme 2). Again, no deoxy analogue was formed in either case.

Scheme 2. Synthesis of *N*-Hydroxy-11-azaartemisin **11** and *N*-Ethanol-11-azaartemisin **12**



Having compound **9** with a free amino group and compounds **11** and **12** with a free hydroxyl group, a stage was set to use these functionalities as handles and convert them into a range of derivatives. Amide derivatives **13a**−**d** were obtained by reacting **9** with benzoyl chloride, *p*-bromobenzoyl chloride, *p*-trifluoromethylbenzoyl chloride, and 4-phenylbenzoyl chloride in dry benzene in the presence of Et_3N at 0 °C in 60−93% yields (Scheme 3, Table 1).

Scheme 3. Synthesis of Amides **13a**−**d**

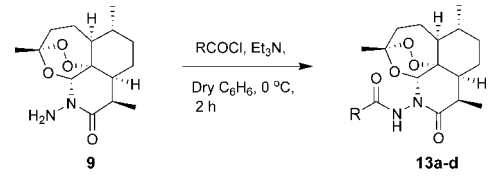
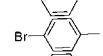
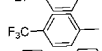


Table 1. Amides **13a**−**d**

entry	R-	yield (%)	mp °C
13a		93	218-220
13b		60	230-232
13c		85	217-220
13d		93	205-207

Under similar conditions, reaction of 2 equiv of **9** with terepthoyl chloride and oxalyl chloride resulted in the

(3) (a) Hindley, S.; Ward, S. A.; Stoor, R. C.; Searle, N. L.; Bray, P. G.; Park, B. K.; Davies, J.; O′Neill, P. M. *J. Med. Chem.* **2002**, *45*, 1052–1063. (b) Woo, S. H.; Parker, M. H.; Ploypradith, P.; Northrop, J.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 1533–1536. (c) Singh, C.; Chaudhary, S.; Puri, S. K. *J. Med. Chem.* **2006**, *49*, 7227–7233. (d) Avery, M. A.; Bonk, J. D.; Chong, W. K. M.; Mehrotra, S.; Miller, R.; Mihous, W.; Coins, D. K.; Venkatesan, S.; Wyandt, C.; Khan, I.; Avery, B. A. *J. Med. Chem.* **1995**, *38*, 5038–5044.

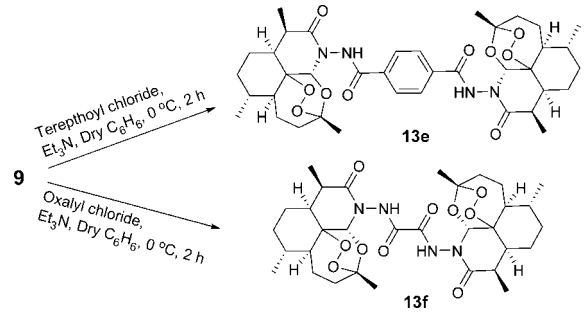
(4) (a) Torok, D. S.; Ziffer, H. *Tetrahedron Lett.* **1995**, *36*, 829–832. (b) Torok, D. S.; Ziffer, H.; Meshnick, S. R.; Pan, X.-Q.; Ager, A. *J. Med. Chem.* **1995**, *38*, 5045–5050. (c) Katz, E.; Ma, J.; Kyle, D.; Ziffer, H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2969–2972.

(5) Haynes, R. K.; Wong, H.-N.; Lee, K.-W.; Lung, C.-M.; Shek, L. Y.; Williams, I. D.; Croft, S. L.; Vivas, L.; Rattray, L.; Stewart, L.; Wong, V. K. W.; Ko, B. C. B. *Chem. Med. Chem.* **2007**, *2*, 1464–1479.

(6) For synthetic 11-aza −9-desmethylartemisinin see Avery, M. A.; Bonk, J. D.; Chong, W. K. M.; Mehrotra, S.; Miller, R.; Mihous, W.; Coins, D. K.; Venkatesan, S.; Wyandt, C.; Khan, I.; Avery, B. A. *J. Med. Chem.* **1995**, *38*, 5038–5044.

formation of dimeric compounds **13e** and **13f** in 20% and 34% yields, respectively (Scheme 4).[8]

Scheme 4. Synthesis of Dimers **13e** and **13f**



Reaction of **9** with benzaldehyde, *p*-bromobenzaldehyde, *p*-trifluoromethylbenzaldehyde, and 4-phenylbenzaldehyde in the presence of Amberlyst-15 as a catalyst in dry benzene at rt furnished the corresponding imines **14a**−**d** in 82−96% yields. Sodium borohydride reduction of imines **14a**−**d** in dry benzene at 0 °C provided amines **15a**−**d**, respectively, in 62−72% yields (Scheme 5, Table 2).

Scheme 5. Synthesis of Imines **14a**−**d** and Amines **15a**−**d**

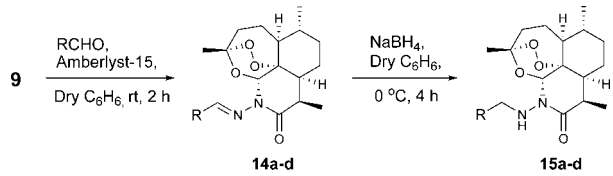
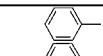
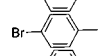
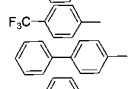
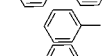
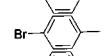
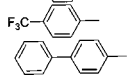


Table 2. Imines **14a**−**d** and Amines **15a**−**d**

entry	R-	yield (%)	mp °C
14a		94	178-181
14b		96	176-178
14c		82	170-173
14d		94	118-120
15a		67	oil
15b		72	152-154
15c		68	137-140
15d		62	68-70

Compound **11** was converted to its ether derivatives **16a**−**d** by reaction with benzyl bromide, (3-bromopropyl)-benzene, 4-phenylbenzyl bromide, and *o*-fluorobenzyl bromide in dry THF in 60−74% yields. Analogous reaction of **12** with benzyl bromide, (3-bromopropyl)benzene, 4-phenylbenzyl bromide, and *o*-fluorobenzyl bromide furnished ethers **17a**−**d** in 62−71% yields (Scheme 6, Table 3).

Scheme 6. Synthesis of Ethers **16a**−**d** and **17a**−**d**

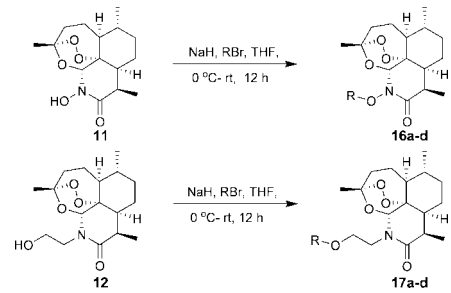


Table 3. Ethers **16a**−**d** and **17a**−**d**

entry	R-	yield (%)	mp °C
16a		72	120-122
16b		60	oil
16c		74	65-66
16d		65	oil
17a		67	oil
17b		64	oil
17c		71	oil
17d		62	oil

While compounds **9**, **11**, and **12** displayed poor antimalarial activity, some of their derivatives have shown a high order of activity against multidrug-resistant *Plasmodium yoelii* in mice by oral route (Table 4).[9] Full activity data will be reported elsewhere.

Table 4. Antimalarial Activity of **9**, **11**, and **12** and Their Derivatives **13d**, **15d**, and **16a** by Oral Route

entry	dose mg/kg × 4 days	% suppression of parasitaemia on day 4	mice survived
9	24	100	2/5
11	48	78.11	0/5
12	48	100	0/5
13d	12	100	5/5
	6	94.37	0/5
15d	12	100	5/5
	6	100	1/5
16a	24	100	5/5
	12	100	2/5
3	48	100	5/5
	24	100	1/5

In conclusion, we have converted artemisinin into three new 11-aza prototypes **9**, **11**, and **12**, with reactive functionalities available to be converted into a wide spectrum of

compounds, some of which have shown a high order of activity against multidrug-resistant malaria in mice.[10]

(7) The reaction of artemisinin with 2-amino ethanol in MeOH has been reported to give only the deoxy analogue of **12**. Reference: Al-Oqail, M. M.; Galal, A. M.; Ahmad, M. S.; Al-Feshawi, A. M.; El-Feraly, F. S. *Molecules* **2003**, *8*, 901–909.

(8) For other dimers of artemisinin see (a) Paik, I.-H.; Xie, S.; Shapiro, T. A.; Labonte, T.; Narducci Sarjeant, A. A.; Baege, A. C.; Posner, G. H. *J. Med. Chem.* **2006**, *49*, 2731–2734. (b) Posner, G. H.; Paik, I.-H.; Chang, W.; Borstnik, K.; Sinishtaj, S.; Rosenthal, A. S.; Shapiro, T. A. *J. Med. Chem.* **2007**, *50*, 2516–2519. (c) Posner, G. H.; Chang, W.; Hess, L.; Woodard, L.; Sinishtaj, S.; Usera, A. R.; Maio, W.; Rosenthal, A. S.; Kalinda, A. S.; D′Angelo, J. G.; Petersen, K. S.; Stohler, R.; Chollet, J.; Santo-Thomas, J.; Snyder, C.; Rottmann, M.; Wittlin, S.; Brun, R.; Shapiro, T. A. *J. Med. Chem.* **2008**, *51*, 1035–1042.

(9) For in vivo antimalarial efficacy test procedure see reference 3c.

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Supporting Information Available: Experimental details and characterization data and purity/characterization Table, ^{1}H NMR and ^{13}C NMR spectra of compounds **9**−**12**, **13a**,**b**,**c**,**d**, **e**,**f**, **14a**−**d**, **15a**−**d, 16a, 16b, 16c, 16d, 17a, 17b, 17c** and **17d.** This material is available free of charge via the Internet at http://pubs.acs.org.

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